REMARKS/ARGUMENTS

Claims 1-6, 8-11, 13-14, 16-17, 19-26, and 28-31are pending. Claims 1, 4, 6, 8, 10, 13, 17, 19, 21, and 26 are amended without prejudice. Claims 8, 30 and 31 are cancelled without prejudice. The specification is amended to insert the generic name "(lactose)" after a trademark. The trademar, "PHARMATOSE," is capitalized. Applicant submits that no new matter is introduced by these amendments.

Objections to the Specification

The Action objects to the specification for including the trademark "Pharmatose." Applicant amends the specification to state the generic name of this compound, lactose, and to capitalize "PHARMATOSE." One of ordinary skill in the art recognizes the trademark Pharmatose, specifically Pharmatose DCL21, as lactose. In addition, the originally filed specficiation states that the "diluents may be water-soluble or water dispersible. Examples of water-soluble diluents that may be used in the present invention include **lactose**, mannitol, glucose, sorbitol, maltose, dextrates, dextrins and the like." Page 9, lines 1-3, bold added. Applicant submits that no new matter is added by the amendment.

Applicant believes that the objection is overcome and respectfully requests withdrawal of the same.

Double Patenting Rejections

U.S. application No. 10/495,961

The Action provisionally rejects claims 1-3, 5-9, 16, 17, and 21 under the doctrine of non-statutory double patenting as unpatentable over claims 30, 37, 39, and 40 of Applicant's co-pending U.S. application No. 10/495,961 (the "961 Application").

Applicant traverses the provisional rejection for at least the following reasons. The '961 application lists the use of a selective hydrophilic polymer mix, essentially of sodium alginate and xanthan gum along with a calcium salt. It is the combination of xanthan gum and sodium alginate in appropriate concentration that controls the initial burst effect. Inclusion of calcium salts provides for controlled release of the active compound and enables maintaining its dissolution characteristics upon storage, at ambient, and accelerated conditions. The invention claimed in the '961 Application leads to improved stability of the pharmaceutical composition.

In the present invention, at least two carbomers are used for the controlled release of cephalosporin antibiotics. These polymers have semi enteric behaviour. At low pH, less than 10% of the carbopol acid groups will be ionized resulting in relatively little swelling leading to hydrogen bonding to polysaccharide and protein

as a major mechanism of bioadhesion to the mucin layer. Thus, the burst effect of the drug in the initial stage is controlled. At higher pH, the carboxylic acid groups are ionized to a greater extent resulting in highly swollen gel formed by electrostatic repulsion of the anionic charges along with the backbone. This reduces hydrogen bonding but increases interaction of polycarboxylate with cationic bases and with polyvalent ions bound on proteins or polysaccharides, which results in bioadhesion in alkaline pH. Thus, controlled release of the drug is achieved.

The Action states that calcium stearate is listed in the '961 application and the instant application. Although calcium salts are generally used for improving stability by maintaining dissolution characteristics upon storage, the '961 Application lists the compound as a lubricant. The '961 Application, page 4, paragraph 41. The instant application also states that calcium stearate as lubricant. However, the parent application, PCT/IN2003/000326, states that carbomers, as recited in the claims of the instant application, are different than polymers like xantham gum.

Applicant notes that neither application has issued and the claims are not necessarily in their final form. Further, Applicant intends to amend the '961 Application claims. When the claims of either application are in their final form, Applicant will determine whether a terminal disclaimer is required.

Applicant respectfully requests withdraw of the provisional obvious type double patenting rejection over the '961 Application.

U.S. Application No. 11/579,988

The Action rejects claims 1, 2, 8, 10, 12, 14, 16, 17, 21, and 28-30 under the doctrine of obviousness type double patenting over claims 1, 6, 10-15, and 17-19 of Applicant's co-pending US patent application No. 11/579,988 (the "'988 Application"). Claim 30 is cancelled and its rejection is moot.

The '988 Application discloses pharmaceutical compositions comprising cefixime trihydrate particles having a mean particle size between 20μ and 120μ exhibiting higher bioavailability and are bioequivalent to suspension formulations. An electronic search of the '988 Application pre-grant publication reveals no instances of "controlled" or "release" and, thus, controlled release of cephalosporins is not mentioned in the '988 Application.

Independent claim 1 recites "at least two carbomers"; independent claims 19 and 21 recite a "combination of at least carbomers"; and independent claim 26 recites a "at least two carbomers". The '988 Application does not list or claim such a composition to achieve the claimed bioequivalent drug release profile of the pharmaceutical formulation. One of ordinary skill in the art would not learn, from the '988 Application, that excipients such as carbomers could be added in order to achieve the claimed composition or the bioequivalent drug release profile.

Applicant respectfully submits that claims 1, 2, 8, 10, 12, 14, 16, 17, 21, and 28-29 of the instant application are entirely different than claims 1, 6, 10-15, and 17-19 '988 application. Based on the differences and the lack of any teaching in the '988 Application related to the claimed invention, claims 1, 2, 8, 10, 12, 14, 16, 17, 21, and 28-29 can not be obvious over the '988 Application. Applicant respectfully requests withdraw of the provisional obvious type double patenting rejection over the '988 Application claims 1, 6, 10-15, and 17-19.

Claim Rejections – 35 USC § 112, 1st Paragraph

The Action rejects claim 22 under 35 U.S.C. §112, first paragraph as failing the written description requirement. As Applicant understands the Action, the Examiner states that since the specific Cmax of the immediate release and delayed release forms are not disclosed, the specification does not support the claims.

The originally filed specification states:

When compared with the conventional immediate release formulation, the bioavailability (AUC) and maximum plasma concentration (Cmax) where found to be comparable as given in Table 2 below.

> The T > MIC at 0.25 mcg/ml was achieved for about 75% of the dosing interval and T > MIC of 2 mcg/ml was achieved for almost 49% of the dosing interval. Both these values are for a time period of more than the 40% of the dosing interval required indicating that it is an excellent controlled release formulation, which not only achieves the desired pharmacodynamic parameters but also manages to maintain the Cmax values substantially similar to those obtained for immediate

release formulations. In fact, the Cmax values were within the 80-120% confidence interval recommended by the US FDA.

Page 17, lines 9-16. There is no requirement that the specification teach that which is routine. As a matter of routine, the skilled artisan would understand not only the data provided but the relative comparison between the immediate and delayed release Cmax values. Based on this description, the skilled artisan would immediately envision what applicant claimed.

Applicant respectfully submits that the 35 U.S.C. §112, first paragrph rejection of claim 22 is improper and requests withdrawal of the same.

Claim Rejections – 35 USC § 112, 2nd Paragraph

Claims 6 and 8

The Action rejects claims 6 and 8 because they recite trademarks. Obviating amendments are made without prejudice. Applicant submits that the rejection of claims 6 and 8 under 35 U.S.C. § 112, second paragraph is overcome and requests withdrawal of the same.

Claims 10, 13, and 17

The Action rejects claims 10, 13, and 17 because they recite "and the like." Obviating amendments are made without prejudice. Applicant submits that the rejection of claims 10, 13, and 17 under 35 U.S.C. § 112, second paragraph is overcome and requests withdrawal of the same.

Claims 30 and 31

The Action rejects claims 30 and 31 because they recite "preferably." Claims 30 and 31 are cancelled and their rejection is moot.

Claim 25 (Claim 22)

The Action rejects claim 25 because it recites "substantially the same." The Action states that the phrase is not defined in the claim nor defined in the specificaiton. Applicant notes that claim 25 does not include this phrase, but claim 22 recites:

> A controlled release composition comprising a cephalosporin antibiotic and a release controlling polymer wherein the C_{max} is substantially the same as that of a single dose of an immediate release formulation.

Underlining added. This is the only claim that recites "substantially the same" and Applicant believes that claim 22 is the proper claim under this heading.

The specification includes guidance to one of ordinary skill in the art that is sufficient to determine the meaning of "substantially the same," as follows:

> The T > MIC at 0.25 mcg/ml was achieved for about 75% of the dosing interval and T > MIC of 2 mcg/ml was achieved for almost 49% of the dosing interval. Both these values are for a time period of more than the 40% of the dosing interval required indicating that it is an excellent controlled release formulation, which not only achieves the desired pharmacodynamic parameters but also manages to maintain the Cmax values **substantially similar** to those obtained for immediate release formulations. In fact, the Cmax values were within the 80-120% confidence interval recommended by the US FDA.

Page 17, lines 9-16, underlining and bold added. Applicant respectfully submits that this passage provides the requisite degree to ascertain the meaning of "substantially the same."

Applicant respectfully submits that the rejection of claim 25(22) under 35 U.S.C. §112, second paragraph is improper and requests withdrawal of the same.

Claim Rejections – 35 USC § 103

Kshirsagar

The Action rejects claims 1-11, 13, 14, 16, 17, 19-26, and 28-31 under 35 U.S.C. § 103(a) as obvious over WO 2004/019901 ("Kshirsagar"). Kshirsagar published March 3, 2004 and was filed August 29, 2003. This application claims priority to PCT/IN03/00326, which was filed September 30, 2003. Claims 7, 30, and 31 are cancelled and their rejection is moot.

Kshirsagar discloses examples relating to controlled release formulations of cefpodoxime proxetil. See pages 19-21. These formulations are prepared using a combination of polymers including carboxymethyl cellulose, carrageenan, polyvinyl pyrrolidone-polyvinyl acetate co-polymer and carbopols as integrity enhancer. The percentage of carbopol used in these compositions is from 0.27% to 1.06%. Claims 1 to 13 relate to controlled release composition using water-soluble polymer N-vinyl 2-pyrrolidone/polyvinyl acetate copolymer and polysaccharide(s) and release enhancers. These claims clearly relate to the use of a combination of polymers for

preparing controlled release, which polymers are entirely different from the ones used in the present invention.

In contrast, the present claims incorporate a combination of at least two grades of carbomers for controlling the release of active ingredient. Independent claims 1, 19, and 21 recite:

> wherein said carbomers are present at a concentration from about 01% to about 50% weight ... .

Further, independent claim 24 recites carbomer with specific properties and claim 26 recites carbomers "from about 0.1-50% by weight." One of ordinary skill in the art would not learn from Kshirsagar that different grades of carbomers could be combined for controlled release, in the recited ranges, or with the recited properties. Kshirsagar uses the polymers in minute amounts as integrity enhancers; *i.e.*, as an additive. Accordingly, Kshirsager does not teach the claimed composition or that at least two carbomers could be used as essential components for controlled release. The claimed inventions cannot be considered as obvious over Kshirsagar and Applicant believes the rejections are overcome and requests withdrawal of the rejections over Kshirsagar.

Katzhendler and Mayron

The Action rejects claims 1-9, 13, 14, 16, 17, 19-26, and 29-31 as obvious over U.S. patent 6,399,086 ("Katzhendler") in view of U.S. patent 3,074,852 ("Mayron"). Claims 7, 30, and 31 are cancelled and their rejection is moot.

Katzhendler discloses controlled release oral drug delivery systems comprising beta lactam antibiotic agent having specific absorption site in the small intestine in combination with polymeric matrix. At least 50% of said beta lactam antibiotic agent are released from said matrix within from about 3 to about 4 hours and the remainder of said pharmaceutical agent is released in a controlled rate. Katzhendler discloses a very specific type of release profile of beta lactam antibiotic providing the desired burst effect followed by controlled release. In order to provide this type of release, a mixture of active antibiotic agent with a pharmaceutically acceptable salt thereof is used as the active pharmaceutical agent in the delivery system (page7, column 4, lines 29-32). Alternatively, granules comprising antibiotic agent and polymer may be prepared and mixed with a powder of the antibiotic agent and compressed into tablets. The free drug would provide the burst effect, while the granules would release the drug contained therein at a constant rate (Column 5, lines 65-67 & Column 6, lines 1-2). Still alternatively, double-layer tablets may be prepared in which one layer would contain the free drug, providing

the burst effect, and the second layer would contain the drug in combination with polymer, providing for controlled release of the active drug (Column 6, lines 3-7).

Katzhendler not disclose the use of carbomer(s) as a polymeric material that is suitable as a delayed release polymer.

In contrast to Katzhendler, the claimed invention includes a controlled release composition of cephalosporin antibiotics with at least two carbomers. The combination of at least two carbomers provides a unique mechanism with a spatial and temporal controlled drug delivery. The mechanism advantageously and effectively utilizes the semi enteric behaviour of carbomers in an acidic enviroment, which controls the initial burst effect and forms a gel at alkaline pH, thereby controlling the drug release by diffusion. This mechanism of drug release using combination of carbomers is completely different from and is not taught by Katzhendler.

Mayron, Example 5, teaches sustained release formulations utilizing a particular grade of Carbopol-934. And the passage relied on by the Examiner, col. 2, ls. 9-12, states "the carboxy vinyl polymer" and preferably "Carbopol 934." Accordingly, Mayron teaches a composition with "the" single polymer. This polymer characteristically provides a zero order release profile of the active ingredient. In the case of cephalosporins, which are preferably absorbed from the proximal part of GIT, Carbopol 934 would not be suitable.

The present application is directed towards a combination of carbomers with unique properties of the two grades. One cabomer, Carbopol 971P in one embodiment, produces a semi enteric effect, whereas other cabomer, Carbopol 974P in one embodiment, on the other hand, provides a prolonged linear release profile. The combination of the two carbomers can be manipulated to achieve the desired drug release profile suitable for the specific needs of cephalosporins. Based on the lack of such a teaching in Mayron, one of ordinary skill in the art would not be motivated to achieve such a release profile. Further, Mayron only discloses the use of one carboxy vinyl polymer, preferably Carbopol 934, and there is no teaching or motivation to use two carbomers as recited in the instant claims.

In addition, Mayron defines the drug to polymer ratio to be at least 1:0.5. Such a ratio is not applicable to the present invention, where the drug to polymer ratio is about 1:0.35. Thus the present formulation is not taught or suggested by Mayron.

In combination, Katzhendler and Mayron do not teach the claim limitations. In order to combine teachings there ought to be reasonable expectation of successes. As set forth above, the mechanism of action disclosed in Katzhendler is different than the mechanism related to the claimed compositions. The only similarity with present invention is the delayed release of beta lactam. Although Mayron teaches a single carbopol for controlled release, there is no motivation for one of ordinary skill

in the art to use two carbomers with betalactum to achieve a release profile discussed above with respect to the claimed composition. The specific release profile in the region of GI tract is not taught or contemplated from the combination and cannot be regarded as optimization. One of ordinary skill in the art would not have looked to Katzhendler, which teaches release of the beta lactam by initial burst, and then to Mayron, which teaches use of single carbomer for controlled release in upper GI tract, to arrive at the claimed composition. In contrast to the composition taught by the cited combination, the claimed composition comprises a beta lactam with a defined release profile with at least two carbomers to effect a prolonged release profile in the GI tract.

Based on the foregoing, Applicant respectfully submits that the 35 U.S.C. 103(a) rejection of claims 1-6, 8-11, 13, 14, 16, 17, 19- 26, and 29 is overcome. Applicant requests withdrawal of the 35 U.S.C. 103(a) rejection of claims 1-6, 8-11, 13, 14, 16, 17, 19- 26, and 29 over Katzhendler in view of Mayron.

Katzhendler, Mayron, and Patel

The Action rejects claims 1, 10, 11, and 28 under 35 U.S.C. §103 as obvious over Katzhendler in view of Mayron and further in view of U.S. patent 6,248,363 ("Patel").

As discussed above, the combination of Katzhendler and Mayron fails to teach the claimed invention and one of ordinary skill in the art would not make the combination to achieve the claimed invention.

Patel does not disclose controlled release compositions of cephalosporins using combination of at least two carbomers and does not overcome the deficiencies of Katzhendler and Mayron. As described in the text at page 10 of the instant specification, and demonstrated in all the examples, the combination of two cabomers is present to provide spatial and temporal control of drug delivery.

Based on the foregoing, Applicant respectfully submits that the 35 U.S.C. 103(a) rejection of claims 1, 10, 11, and 28 is overcome. Applicant requests withdrawal of the 35 U.S.C. 103(a) rejection of claims 1, 10, 11, and 28 over Katzhendler in view of Mayron and further in view of Patel.

Conclusion

If the Examiner believes that any additional matters need to be addressed in order to place this application in condition for allowance, the Examiner is invited to contact the undersigned by telephone at the Examiner's convenience.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application, including claims 1-6, 8-11, 13-14, 16-17, 19-26 and 28-29, is in condition for allowance and a notice to that effect is respectfully requested.

Respectfully submitted,

Shailesh Bhamare

By:/Douglas J. Bucklin/
Douglas J. Bucklin, Ph.D.
Registration No. 51,208

Volpe and Koenig, P.C.
United Plaza, Suite 1600
30 South 17th Street
Philadelphia, PA 19103
Telephone: (215) 568-6400
Facsimile: (215) 568-6499

DJB/dml